Effect of IBS Type on Alosetron-Induced Withdrawal for Constipation

Treatment	Patient Number: sex/age/race	Predominant Type of IBS by history	Baseline Stool Consistency Score	Days on Drug
Placebo	F0633: M32c	Alternating	2.64	14
	F0661: F38c	Alternating	2.91	27
Alosetron 0.1 mg BID	F0329: F34c	Alternating	2.33	36
	F0373: F67c	Diarrhea	3.15	15
	F0686: F35c	Constipation	2.69	15
Alosetron 0.5 mg BID	F0239: F45c	Constipation	3.47	15
	F0240: F52c	Constipation	1.64	15
	F0523: F55c	Constipation	4.07	28
	F0735: F43c	Constipation	3.38	57
	F0818: M55c	Constipation	1.55	16
	F0830: F30c	Constipation	2.63	54
	F1015: F42c	Alternating	2.67	15
	F1078: F20c	Diarrhea	3.44	15
Alosetron 2.0 mg BID	F0161: F45b	Constipation	2.29	69
	F0245: F37c	Constipation	1.58	15
	F0681: M39c	Constipation	2.69	54
	F0684: F64c	Constipation	3.25	17
	F0688: F60c	Constipation	2.91	21
	F0738: F56c	Alternating	3.31	13
	F0857: F68c	Constipation	2.62	21
	F0997: F46c	Constipation	2.50	58
	F1029: F57c	Diarrhea	3.29	35

Comment: . Alosetron seldom caused enough constipation to force withdrawal in diarrhea-prone patients, but sufficient doses were a problem in patients with a history of constipation, even if not present at the moment. Although men constituted 27% of the safety population, only 3 of the 22 patients who were withdrawn for constipation were male (13.6%), a disproportionately lower proportion than for women, who appeared more prone to develop constipation troubling enough to make them withdraw from study. Demographic data for these patients were taken from the listings in Volume 204, pages 1-65. It was also observed, in retrospect, that the beneficial effects on IBS that was indicated by this study was only seen in women; men showed no significant benefit over placebo from any dose of alosetron given (Appendix 22, Volume 202, page 357-77).

No pregnancies were reported in any of the women during their participation in this study. No significant differences in laboratory values for blood chemistry, hematology, or urinalysis were found between groups of patients on placebo or any of the alosetron doses. Five patients were found to have elevated serum values for liver enzymes, one each on placebo, and the two lower doses of alosetron, and two on alosetron 2 mg b.i.d. The patient on placebo (F0162) was later found to have acute hepatitis C, the patient on alosetron 0.5 mg b.i.d. (F0794) was withdrawn, and the other three (F0905; F0313 and F0314) were listed as adverse events.

Comment: Individual data for the abnormal serum levels of liver enzymes were not provided, nor were individual levels of serum bilirubin or albumin or blood prothrombin, so no correlations could be made. No details were provided in Appendix 18 or 19 (Volume 201, pages 329-49. A copy of the CRF was provided for only one of the patients, F0794, a 48-year-old _____ woman who developed rising values of serum alanine aminotransferase, glutamyl transferase, and aspartate aminotransferase but not of serum bilirubin, over the first 4 weeks of study and then was withdrawn. A note on the withdrawal sheet said that the elevated values returned toward normal, but rose again later even without any further alosetron.

Adverse Events, General

When adverse events (AEs) that were neither serious nor causing withdrawal were considered, again the same story was apparent. About half the patients in each of the study groups had at least one AE, but there was no significant difference in the total number of events nor patients who had them between study groups:

Patients Showing Adverse Events, Study S3BP12

	Placebo BID n = 117	A 0.1 mg BID n = 115	A 0.5 mg BID n = 116	A 2.0 mg BID n = 114
Pre-treatment (2 weeks)				
Any adverse event	4 (3.4%)	10 (8.7%)	14 (12.1%)	7 (6.1%)
During treatment (12 weeks)				
Any adverse event	60 (51.3%)	56 (48.7%)	63 (54.3%)	64 (56.1%)
Gastrointestinal event	**22 (18.8%)**	**26 (22.6%)**	**34 (29.3%)**	**36 (31.6%)**
Constipation	**3 (2.6%)**	**5 (4.3%)**	**15 (12.9%)**	**19 (16.7%)**
GI or Abdominal pain	8 (6.8%)	6 (5.2%)	10 (8.6%)	9 (7.9%)
Nausea or vomiting	6 (5.1%)	5 (4.3%)	10 (8.6%)	12 (10.5%)
Neurological event	28 (23.9%)	19 (16.5%)	19 (16.4%)	20 (17.5%)
Headaches	22 (18.8%)	14 (12.2%)	14 (12.1%)	12 (10.5%)
Hypnagogic effects	1 (0.9%)	1 (1.7%)	2 (1.7%)	4 (3.5%)
Cardiovascular event	2 (1.7%)	2 (1.7%)	4 (3.4%)	1 (0.9%)
Arrhythmias	0	1 (0.9%)	1 (0.9%)	0
Malaise or fatigue	8 (6.8%)	6 (5.2%)	5 (4.3%)	3 (2.6%)
Psychiatric event	1 (0.9%)	1 (0.9%)	2 (1.7%)	2 (1.7%)
Musculoskeletal event	5 (4.3%)	4 (3.5%)	7 (6.0%)	11 (9.6%)
Pain or discomfort	3 (2.6%)	3 (2.6%)	3 (2.6%)	7 (6.1%)
Post-treatment (4 weeks)				
Any adverse event	8 (6.8%)	10 (8.7%)	7 (6.0%)	8 (7.0%)

Comment: Again noted, the main significant difference between treatment groups is seen to be in adverse gastrointestinal events on the two higher doses of alosetron, compared to placebo, particularly the highly significant and clearly dose-related increase in constipation. Headaches and cardiac arrhythmias were not a problem. Increased musculoskeletal pain and nausea/vomiting on the highest alosetron dose used are noted, appeared to suggest a dose-response effect (even though not significant because of the small numbers), and will be compared in the other studies.

2. S3BA2001: U.S. 12-week, placebo-controlled, dose-ranging study

The second dose-ranging study was carried out at 68 centers, principally in the United States but also at a few centers in Canada, England, Germany, and Holland, from October 1995 to December 1996. A total of 835 adults with histories of IBS for at least 6 months, by Rome criteria, were screened to find 370 (112 men, 258 women) with normal sigmoidoscopy or colonoscopy results, moderately severe pain/discomfort scores (from 1.5 to 3.3) and average stool consistency scores of at least 2.5, who were willing to participate and met all the entry criteria. The median age of the patients was 43 years, ranging from 18 to 94; most of the patients (94%) were Caucasian, 2.7% Black, 2.4% Hispanic, 0.08% Oriental or Other. They were randomized to five double-blinded treatment groups, to receive b.i.d. doses (before breakfast and supper) of 1, 2, 4, 8 mg of alosetron or placebo. There were no statistically significant differences between the randomized groups with respect to gender, race, age, height or weight distribution, in duration of IBS, nor in use of tobacco or alcohol, and for the women, in menopausal status or use of estrogenic substances. The patients screened but rejected showed similar distributions of demographic characteristics except for a higher percentage (8%) of Hispanics (Volume 110, pages 187-94).

A total of 835 patients were screened, 465 or almost 56% of whom were rejected as not eligible for randomization, most (395) because entry criteria were not met, but 27 withdrew consent, 16 failed to return, 3 had adverse events, and 24 offered a variety of other reasons, many of which were redundant (volume 110, page 172 and Volume 115, pages 93-109). Of the 370 patients randomized with intent to treat (ITT), 4 were screened, accepted, and randomized but took no study medication (belatedly ineligible), resulting in 366 for the safety population sample.

Disposition of Patients Randomized into Study S3BA2001

	Placebo BID	A 1 mg BID	A 2 mg BID	A4 mg BID	A 8 mg BID	Total
Patients randomized	80	72	74	76	68	370
men/women	21/59	19/53	23/51	21/55	28/40	112/258
Sub-type of IBS						
diarrheal	41(51%)	37(51%)	43(58%)	51(67%)	35(51%)	207(56%)
alternating	30(38%)	26(36%)	26(35%)	23(30%)	27(40%)	132(36%)
constipative	9(11%)	9(13%)	3(4%)	2(3%)	5(8%)	28(8%)
Took no medication	0	-2	-1	-1	0	-4
Safety set	80	70	73	75	68	366
Withdrawn prematurely	-12 (15.0%)	-15 (20.8%)	-22 (29.7%)	-20 (26.3%)	-20 (29.4%)	-89 (24.1%)
adverse event	-5	-4	-17	-10	-13	-49
no stool, 7 days	0	-4	-1	-1	-4	-10
lack of efficacy	-2	-2	0	-4	-2	-10
withdrew consent	-3	-1	0	1	-1	-6
failed to return	-1	-2	-3	0	0	-6
other	-1	-2	-1	-4	0	-8
Completed study	68	57	52	56	48	281

Note: A, alosetron; BID, twice daily, before breakfast and supper.

Comment: It was not made clear how the 28 patients with constipation-predominant IBS were in the study, nor was it listed as a protocol violation in Table 4.0 (volume 110, page 180).

The stated purpose of this study (Volume 110, page 37) was to determine the lowest effective and best tolerated dose of alosetron, and to define endpoints for subsequent confirmatory pivotal studies. Patient reporting hard or very hard stools, on average during screening, were considered to have constipation-predominant IBS and were not eligible to enter. The study size was based on assuming five equal treatment arms, an expected 26% dropout rate, an expected response of 18% days free of pain/discomfort during placebo treatment and 40% on some dose of alosetron, with 95% power to detect a difference significant at $\alpha = 0.05$. According to the protocol (volume 110, pages 115-7) 70 patients per group would be required, or 350 in total.

Deaths and Serious Adverse Events

There were no deaths among the patients reported during or immediately after the study. There were 9 adverse events classified as serious, 3 of which caused withdrawal* from the study:

Serious Adverse Events, Study S3BA2001 *(Vol. 110, pages 162-70)*

Dose, mg b.i.d.	*Patient number: sex/age/race*	*Clinical Problem After __ time on study drug*	*Investigator's Opinion*
Placebo	42638:2670 F27c	Ovarian cyst rupture @ 12+ weeks	unrelated
	4850:2503 F35c	Ovarian cyst @ 3 weeks	unrelated
Alosetron 1 mg	42823:0768 F20c	Acute tonsillitis @ 11 days	unrelated
Alosetron 2 mg	3336:2443 F65c	Acute diverticulitis @ 12 days*	unlikely related
	42616:2829 F33c	***Acute "ischemic" colitis @ 2 days****	unlikely related *?*
Alosetron 4 mg	2265:2396 F59c	Severe angina pectoris @ 8 weeks	unrelated
	5668:2480 M49c	Angina pectoris @ 10 days	unrelated
Alosetron 8 mg	42824:0778 F56c	Angina @ 3 days	unrelated
	5438:2063 F61c	Acute diverticulitis @ 6 weeks*	unlikely related

Note: M, male; F, female; c, Caucasian.

Comment: All of these cases were considered by investigators as "unrelated" to study drug, which may be reasonable for the two women with pre-existing ovarian cysts that caused trouble while they were taking placebo or shortly afterward, the young woman with acute tonsillitis (known before study), and for the three patients with cardiac pain, all of whom had histories of prior cardiovascular disease. However, it might be questioned whether alosetron, with its known constipating effects, could have played a role in the two cases of acute diverticulitis and the acute undiagnosed colitis attributed to ischemia (but with no preceding hypotension or circulatory problems in a 33-year-old woman). Again, the copies of the CRFs submitted as .pdf files on tape failed to include 5 of the 9 cases who had SAEs.

The number of patients withdrawn prematurely was again substantial, 89 of 370 (24%), which was close to the 26% estimated in the protocol and study size calculation. Reasons given for these premature withdrawal were as above. The leading reason for premature withdrawal was adverse events, accounting for over half (55%) of all withdrawn; not included in that were patients withdrawn because they had no stool for at least a week, another 11%. In addition, 7% "withdrew consent" and 7 % "failed to return", and the category of "other" in 9%. Listing DL-4 (Volume 115, pages 130-50) provides statements of the reasons for withdrawal, which in several cases shows "Other: consent withdrawn" tabulated as "Consent withdrawn" rather than "Other." The adverse events for which patients were withdrawn are listed in Volume 110, pages 320-7.

Adverse Events Causing Premature Withdrawal, S3BA2001

	Placebo BID n = 80	A 1 mg BID n = 70	A 2 mg BID n = 73	A 4 mg BID n = 75	A 8 mg BID n = 68
Withdrawn prematurely	12 (15.0%)	15 (21.4%)	22 (30.1%)	20 (26.7%)	20 (29.4%)
Any adverse event	5 (6.3%)	8 (11.4%)	18 (24.7%)	11 (13.3%)	17 (25.0%)
Gastrointestinal event	**4 (5.0%)**	**7 (10.0%)**	**17 (23.3%)**	**9 (12.0%)**	**16 (23.5%)**
constipation	**2 (2.5%)**	**7 (10.0%)**	**12 (16.4%)**	**8 (10.7%)**	**13 (19.1%)**
Neurological event	1 (1.3%)	2 (2.9%)	1 (1.4%)	1 (1.3%)	1 (1.5%)
headache	1 (1.3%)	2 (2.9%)	1 (1.4%)	0	1 (1.5%)
Cardiovascular event	0	0	1 (1.4%)	0	0
arrhythmias	0	0	0	0	0

Note: BID, twice daily; A, alosetron.

Comment: Again noted, there was an alosetron dose-related increase in the number of adverse events, nearly all of with were gastrointestinal, and a highly significant dose-related increase in constipation in patients on alosetron. Headaches and arrhythmias were not a problem in this study, and no other single adverse event was notable outside of those of constipation.

Adverse Events, General

When adverse events (AEs) that were neither serious nor that caused withdrawal were considered, again the same story was apparent.

Patients Showing Adverse Events, Study S3BA2001

	Placebo BID n = 80	A 1 mg BID n = 70	A 2 mg BID n = 73	A 4 mg BID n = 75	A 8 mg BID n = 68
During 12-week treatment					
Any adverse event	49 (61.3%)	47 (67.1%)	46 (63.0%)	54 (72.0%)	50 (73.5%)
Gastrointestinal event	**22 (27.5%)**	**25 (35.7%)**	**29 (39.7%)**	**31 (41.3%)**	**34 (50.0%)**
Constipation	**5 (6.3%)**	**14 (20.0%)**	**19 (19.4%)**	**15 (20.0%)**	**20 (29.4%)**
GI or Abdominal pain	6 (7.5%)	8 (11.4%)	5 (6.8%)	8 (10.7%)	10 (14.7%)
Nausea or vomiting	11 (13.8%)	5 (7.1%)	10 (13.7%)	9 (12.0%)	4 (5.9%)
Neurological event	24 (30.0%)	12 (17.1%)	8 (11.0%)	11 (14.7%)	12 (17.6%)
Headaches	16 (20.0%)	8 (11.4%)	7 (9.6%)	5 (6.7%)	9 (13.2%)
Cardiovascular event	5 (6.3%)	1 (1.4%)	4 (5.5%)	2 (2.7%)	2 (2.9%)
Arrhythmias	1 (1.3%)	0	1 (0.9%)	0	1 (1.5%)
Malaise or fatigue	4 (5.0%)	3 (4.3%)	5 (6.8%)	2 (2.7%)	6 (8.8%)
Psychiatric event	3 (3.8%)	3 (4.3%)	2 (2.7%)	1 (1.3%)	2 (2.9%)
Musculoskeletal event	4 (5.0%)	10 (14.3%)	4 (5.5%)	4 (5.3%)	8(11.8%)
Pain or discomfort	3 (3.8%)	7 (10.0%)	3 (4.1%)	3 (4.0%)	4(5.9%)

Note: BID, twice daily; A, alosetron

Comment: Over half of the patients in each study group had at least one AE, with no significant difference in the total number of events or number of patients who had them (Volume 110, pages 299-309). Again, there were significantly more adverse gastrointestinal events on all doses of alosetron, particularly the highly significant and clearly dose-related increase in constipation in patients taking alosetron. No problems were seen with arrhythmias, headaches, nausea/vomiting, or musculoskeletal pain, beyond those in the placebo-treated group.

C. Principal U.S. efficacy studies in women only

1. S3BA3001: 12-week, placebo-controlled study in women

The two confirmatory, "pivotal" clinical studies that followed the dose-ranging studies in Europe and the United States were designed with identical protocols, and carried out using the established dose of 1 mg alosetron b.i.d. before breakfast and before the evening meal, in women only, and excluding women with constipation-predominant IBS. This restriction to a defined subset of patients with IBS followed the data resulting from the dose ranging studies S3BP12 and S3BA2001 in which it was discovered that men did not benefit from the dose of 1 mg b.i.d. that seemed to help women, especially those with diarrhea-predominant IBS. The retrospective redefinition of an endpoint as "adequate relief" of IBS symptoms resulted from the failure to see a significant reduction in the fraction of pain-free days in patients on alosetron in S3BA2001; this was reduced to a secondary efficacy measure in the protocols for S3BA3001 and -3002.

It was estimated that 300 patients for each of two study arms, 600 in all, would be needed to detect with 90% power at two-sided $\alpha = 0.05$ significance an increase of 15% in the proportion of patients on alosetron 1 mg b.i.d. who had "adequate relief" to about 55%, compared to 40% on placebo, allowing for 20% dropouts. (Volume 138, page 59). Patients were to be adult women with IBS fulfilling Rome criteria (abdominal pain/discomfort relieved by defecation or associated with change in stool frequency or consistency for at least 6 months, and at least a 6-month history at least 2 days/week of > 3 stools/day or < 3/week; stools either lumpy-hard or loose-watery; straining or urgency or feeling of incomplete evacuation; passage of mucus; or bloating or distention). In addition, they had to show by daily telephone report during a two-week (at least 12 days) screening period pain/discomfort of moderate average severity (1.0 to 3.3 on a pain scale of 0 = none, 1 = mild, 2 = moderate, 3 = intense, and 4 = severe), and average stool consistency of at least 2.5 (on a scale of 0 = none, 1 = very hard, 2 = hard, 3= formed. 4 = loose, and 5 = watery). The women had to have had a normal sigmoid/colonoscopy, not have any major other system disease or any organic gastrointestinal disorder, not be using any of a long list of prohibited drugs affecting gastrointestinal motility or perceptions of pain. Data were to be gathered daily by touch-tone telephone in response to preprogrammed standard questions, and weekly questioning as to whether they had adequate relief the previous week (developed and analyzed by [redacted]. Adverse events were assessed by the investigators at visits at 4-week intervals during and once after the 12-week of study drug administration.

Of 1417 patients screened, 791 (56%) were excluded because pain severity or stool consistency scores were not met during the two-week screening period in 475 (low stool consistency score in 200, low pain score in 175, both in 78, high pain score in 20, and both high pain and low consistency scores in 2), other criteria were not met in 165, consent was withdrawn in 102, 19 failed to return, 5 had adverse events, and 25 had other miscellaneous reasons (Table s-6.1, Volume 138, page 132). This left 626 women who were randomized, 309 to alosetron 1 mg and 317 to placebo b.i.d. A dropout rate of 23% was observed, 143 women leaving the study prematurely for a variety of reasons, principally adverse events , but substantial numbers also for "consent withdrawn" or "lost to follow-up" or "other" reasons. Study participants had a median age of 46 years, ranging from 18 to 83, were 88% Caucasian, 7% Black, 5% Hispanic, <1% Asian, and <1% Other. There were no significant differences in distribution of age, race, height,

weight, childbearing potential/menstruation, or use of estrogens between study groups. The study was carried out at 115 U.S. centers, from 18 September 1997 to 18 December 1998.

Disposition of Patients Randomized into Study S3BA3001

	Placebo BID	A 1 mg BID	Total
Patients randomized	317	309	626
men/women	0/317	0/309	0/626
Sub-type of IBS			
diarrheal	222 (70.0%)	224 (72.5%)	446 (71.2%)
alternating	87 (27.4%)	82 (26.5%)	169 (27.0%)
constipative	8 (2.5%)	3 (1.0%)	11 (1.8%)
Withdrawn prematurely	-71 (22.4%)	-72 (23.3%)	-143 (22.8%)
adverse event	**-21 (6.6%)**	**-48 (15.5%)**	**-69 (11.0%)**
lack of efficacy	-7 (2.2%)	-7 (2.3%)	-14 (2.2%)
withdrew consent	-25 (7.9%)	-6 (1.9%)	-31 (5.0%)
lost to follow-up	-11 (3.5%)	-6 (1.9%)	-17 (2.7%)
other	-7 (2.2%)	-4 (1.3%)	-11 (1.8%)
protocol violation	0	1 (0.3%)	1 (0.2%)
pregnancy	1 (0.3%)	0	1 (0.2%)
death	0	0	0
Completed study	246 (77.6%)	237 (77.0%)	483 (77.2%)

Note: A, alosetron; BID, twice daily, before breakfast and supper.

Comment: It is noteworthy that there should be significantly ($p < 0.0005$) more patients who withdrew consent or were lost to follow-up in the placebo group, 36 (11.4%) than in the group treated with alosetron, 12 (3.9%). The question again arises as to whether this quite significant difference might mask adverse events or lack of efficacy. The increase in adverse events in the alosetron-treated group over that in the placebo-treated group is also statistically very significant ($p < 0.0005$). However, there is no way retrospectively to analyze more thoroughly the reasons perhaps for why patients "withdrew consent" or chose to be "lost to follow-up," if those pseudo-reasons were accepted by study personnel and no further inquiry pursued.

The dropout rate of 23% was somewhat higher than the 20% predicted in the estimated study size calculation, but was consistent with the rate of 24% in S3BA2001. In studies such as this, involving a capricious, intermittent but chronic disorder, whose symptoms wax and wane in response to so many factors and are so often self-limited (read placebo response), it is very important to decrease the uncertainty of studies by reducing dropouts and incomplete data collection to a minimum. It is noted that a few patients with constipation-predominant IBS did slip through the screening process, 11 of the 626 randomized patients (1.8%), despite the exclusion of disproportionately larger fractions of constipation-prone and alternately types of IBS in the group of 791 excluded during screening (9% constipation-predominant, 38% alternating IBS), as listed in Table S-6.9, Volume 138, page 147.

When the effect of the preceding perceived type of IBS was considered, comparisons of withdrawals from study of the three subsets showed (Volume 138, pages 72-3):

Withdrawals from Study S3BA3001, by IBS Sub-type

Reasons for Premature Withdrawal from Study	Placebo BID n = 317	Alosetron 1 mg BID n = 309	Total n = 626
Diarrhea-predominant IBS	222 (70.0%)	224 (72.5%)	446 (71.2%)
All withdrawals	54	55	109
Adverse events	**19**	**38**	**57**
Consent withdrawn	17	4	21
Lost to follow-up	8	4	12
Lack of efficacy	5	6	11
Protocol violation	0	1	1
Other reason	5	2	7
Alternating type of IBS	87 (27.4%)	82 (26.5%)	169 (27.0%)
All withdrawals	14	16	30
Adverse events	**1**	**9**	**10**
Consent withdrawn	7	2	9
Lost to follow-up	3	2	5
Lack of efficacy	2	1	3
Protocol violation	0	0	0
Other reason	1	2	3
Constipation-predominant IBS	8 (2.5%)	3 (1.0%)	11 (1.8%)
All withdrawals	3	1	4
Adverse events	**1**	**1**	**2**
Consent withdrawn	1	0	1
Lost to follow-up	0	0	0
Lack of efficacy	0	0	0
Protocol violation	0	0	0
Other reason	1	0	1

Comment: The disparity in withdrawals for adverse events is even magnified further in those with the constipation-diarrhea alternating type of IBS, although the number are small.

Deaths and Serious Adverse Events

There was 1 death that occurred before this study, of patient #4129, a 42-year old Caucasian woman, who was severely depressed and committed suicide by shooting herself in the heart during the screening phase before randomization. She took no study drug, and was not included in the intent to treat, and no inference can be drawn that her death was alosetron-related.

There were 12 adverse events classified as serious that occurred during or shortly after the 12-week treatment phase, 4 of which led to withdrawal* from the study. In addition, one patient, #5141 a 24-year-old Caucasian woman, became pregnant after 2 weeks on placebo and was withdrawn from the study and then lost to follow-up. Additional cases of serious AEs occurred in several (6) patients during the screening period before initiation of study drug treatment, but could not be alosetron-related. One patient #4507, a 39-year-old Caucasian woman with diarrhea-

predominant IBS, was randomized to placebo but never took any study drug and was not included in the safety analyses, leaving 316 placebo- and 309 alosetron-treated women in the safety subset of 625 patients. Narrative summaries are provided for the cases in Volume 138, pages 117-25.

Serious Adverse Events, Study S3BA3001 *(Vol. 138, pages 103-5, 117-25)*

Dose, mg b.i.d.	*Patient no. & age/sex/race*	*Clinical Problem After __ time on study drug*	*Investigator's Opinion*
Placebo	4350 45Fc	Herniated C5-C6 disc @ 3 days	unrelated
	4384 77Fc	Severe angina pectoris @ 6 weeks	unrelated
	4960 39Fb	Asthmatic attack @ 8 weeks*	unrelated
	4989 51Fc	Severe chest pain @ 10 weeks	unrelated
	5625 64Fb	Unstable angina @ 4 weeks	unrelated
	5759 44Fb	Chest pain @ 7 weeks	possibly related
Alosetron 1 mg	4163 20Fc	Acute viral gastroenteritis @ 9 weeks*	unrelated
	4190 53Fc	Acute viral gastroenteritis @ 6 weeks	unrelated
	4445 56Fc	Acute pancreatitis @ 13 weeks	unrelated
	4595 33Fc	Post-ERCP pulmonary edema @ 11 weeks*	unrelated
	5079 66Fc	Non-cardiac chest pain @ 7 weeks	unrelated
	6041 43Fb	Asthmatic attack @ 15 weeks	unrelated
	15687 41Fc	***Ischemic colitis @ 8 weeks****	**possibly related**

Note: M, male; F, female; c, Caucasian; b, Black.

Comment: There was no significant difference in the proportions of patients with SAEs between the two treatment groups: 6/316 (1.9 %) on placebo and 7/309 (2.3 %) on alosetron, p > 0.4, and two of the patients randomized to alosetron had their SAEs after the study was over. Copies of case reports as .pdf files were provided for only 4 (patients # 4445, 4595, 4960, 15687) of the 13 patients who had SAEs listed above.

From examination of the CRFs and narratives, two of the alosetron patients deserve further comment and discussion:

Patient #15687, [redacted] a 41-year-old Caucasian women, overweight (body mass index 29.7 kg/m²) but not diabetic and with normal screening laboratory values and flexible sigmoidoscopy before randomization, presented at her local emergency room on the 54th day of treatment with alosetron 1 mg b.i.d with rectal bleeding and abdominal pain. She did not respond to hyoscyamine treatment and was hospitalized for investigation the next day. Severe segmental colitis was seen by colonoscopy the following day, with shallow and irregular ulcerations of the mucosa extending from mid-transverse to the proximal sigmoid colon. This was thought to be due either to Crohn's colitis or possibly to ischemic colitis. There had been no prior suggestion of atherosclerotic vascular disease nor a precipitating circulatory event of hypotension or reduced cardiac output. Biopsy of the affected mucosa was consistent with ischemic colitis but not Crohn's disease.

Patient #4595, [redacted] a 33-year-old Caucasian woman, overweight (body mass index 29.4 kg/m²) and depressed (on Prozac), had an episode of serious and severe pulmonary edema immediately after an endoscopic retrograde cholangiopancreatographic (ERCP) procedure under general anesthesia, for which she was hospitalized and treated for a week. This complication was considered unrelated to study drug by the investigator. However, when the record is further examined for why she had the ERCP done, it is noted that she had had an earlier

transient elevation of her serum enzymes and total bilirubin after 22 days on alosetron, and for which the study drug was stopped on the 50th day, with resolution of the abnormalities, a sequence of events that the investigator considered quite possibly study drug-induced. This event was considered non-serious because it was not life threatening nor was hospitalization required. It did lead, however, to a serious complication following the uninformative ERCP. The CRF does show a most informative sequence of laboratory data, all but one set (22 Apr 98) of which were done by the central laboratory of the study ( ). There was no liver biopsy, and no rechallenge done.

Serial Hepatotoxicity Tests for Patient #4595

Test (NR) Date (1998)	*ALT 6-34 IU/L*	*AST 9-34 IU/L*	*AlkPhos 31-110 IU/L*	*Total Bili 0.2-1.2 mg/dL*	*comment*
09 Feb	*21*	*26*	*103*	*0.5*	*screening*
27 Feb					*start drug*
20 Mar	***65***	***62***	***198***	*0.4*	*22nd Day*
17 Apr	***131***	***111***	***174***	***2.1***	*50th Day*
20 Apr					*stop drug*
22 Apr	*75*	***38***	***156***	*1.1*	*off 2 days*
01 May	*29*	*10*	*90*	*0.7*	*off 11 days*
15 May					*ERCP done*

Note: NR, normal range; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AlkPhos, alkaline phosphatase; Bili, bilirubin; IU/L, international of enzyme activity per liter of serum.

The adverse events for which patients were withdrawn are listed in Volume 138, pages 425-7.

Adverse Events Causing Premature Withdrawal, S3BA3001

patients	Placebo BID n = 316	A 1 mg BID n = 309	Difference p-value
Withdrawn prematurely	71 (22.5%)	72 (23.3%)	N.S.
Any adverse event	**21 (6.7%)**	**48 (15.5%)**	**<0.0005**
Gastrointestinal event	**13 (4.1%)**	**45 (14.6%)**	**<<0.0001**
constipation	**5 (1.6%)**	**32 (10.4%)**	**<<0.0001**
all other gi events	8 (2.5%)	13 (4.2%0	N.S.
Neurological event	2 (0.6%)	3 (1.0%)	N.S.
headache	1 (1.3%)	2 (2.9%)	N.S.
Cardiovascular event	1 (0.3%)	0	N.S.
arrhythmias	0	0	N.S.
Malaise or fatigue	2 (0.6%)	4 (1.3%)	N.S.
All other system AEs*	11 (3.5%)	8 (2.6%)	N.S.

*Note: BID, twice daily; A, alosetron; *, some patients had more than one AE.*

Comment: Very significant differences were found between treatment groups in the relative numbers of patients withdrawn from study because of adverse events, due almost entirely to gastrointestinal events and particularly if not entirely to constipation. These findings reconfirmed the findings made repeatedly before.

Adverse Events, General

Considering all AEs, regardless of whether they were serious or caused withdrawal (Table T-9.2, Volume 138, pages 412-20):

Patients Showing Adverse Events, Study S3BA3001

Patients Showing, during 12-week treatment	Placebo BID n = 316	A 1 mg BID n = 309	Difference p-value
Any adverse event	**208 (65.8%)**	**233 (75.4%)**	**0.011**
Gastrointestinal event	**96 (30.4%)**	**155 (50.2%)**	**< 0.001**
Constipation	**21 (6.6%)**	**80 (25.9%)**	**<< 0.0001**
GI or Abdominal pain	19 (6.0%)	27 (8.7%)	N.S.
Nausea or vomiting	26 (8.2%)	33 (10.7%)	N.S.
Neurological event	45 (14.2%)	49 (15.9%)	N.S.
Headaches	28 (8.9%)	28 (9.1%)	N.S.
Cardiovascular event	12 (3.8%)	11 (3.6%)	N.S.
Arrhythmias	2 (0.6%)	2 (0.6%)	N.S.
Malaise or fatigue	12 (3.8%)	11 (3.6%)	N.S.
Psychiatric event	9 (2.8%)	13 (4.2%)	N.S.
Musculoskeletal event	37 (11.7%)	39 (12.6%)	N.S.
Pain or discomfort	20 (6.3%)	21 (6.8%)	N.S.
Lower respiratory	27	22	N.S.
Endocrine/Metabolic	16	13	N.S.
Hepatobiliary/pancreatic	3	5	N.S.
Blood & Lymphatic	0	4	p = 0.059
Urologic	12	20	N.S.
Reproductive	20	14	N.S.
Skin	20	15	N.S.
Eye	5	7	N.S.
Ear, Nose & Throat	57	59	N.S.
Non-Site Specific	47	36	N.S.
Trauma/Overdose	13	9	N.S.

Note: BID, bis in die, twice daily; A, alosetron

Comment: The significant increase in adverse events was due almost entirely to more constipation in patients taking alosetron, with no other adverse event showing significant differences between treatment groups.

The applicant company, in planning these pivotal trials, had become fully aware of the problem of alosetron-induced constipation, particularly in patients with IBS not of the frankly diarrheal type. To reduce problems in the study patients, both protocols included provisions for study drug interruption for 4 days if the patient had no stools for 4 consecutive days; if stools returned at or within the 4 days of drug interruption, blinded treatment could resume after the 4-day interruption, but if not and the person had no stool for 8 days, the drug was to be stopped and the participant withdrawn from study because of constipation. This interruptive cycle could be repeated if necessary, and study participation continued. When results of this procedure were analyzed (Tables D-9.7, A-9.7, Volume 138, pages 445-7):

Interruption of Study Drug Because of Constipation, Study S3BA3001

	Placebo BID	A 1 mg BID	Total	Difference p-value
All participants	*n = 316*	*n = 309*	*n = 625*	
at least 4 days without stool	15	43	58	*p = 0.0001*
1 cycle	10	32	42	
2 cycles	3	5	8	
>2 cycles	2	4	6	
8 days without stool	0	2	2	
Diarrhea-predominant	*n = 221*	*n = 224*	*n = 445*	
at least 4 days without stool	11	28	39	*p < 0.01*
1 cycle	8	22	30	
2 cycles	1	4	5	
>2 cycles	2	1	3	
8 days without stool	0	1	1	
Alternating type of IBS	*n = 87*	*n = 82*	*n = 169*	*p <0.01*
at least 4 days without stool	4	14	18	
1 cycle	2	9	11	
2 cycles	2	1	3	
>2 cycles	0	3	3	
8 days without stool	0	1	1	
Constipation-predominant	*n = 8*	*n = 3*	*n = 11*	
at least 4 days without stool	0	1	1	*N.S.*
1 cycle	0	1	1	
2 cycles	0	0	0	
>2 cycles	0	0	0	
8 days without stool	0	0	0	

Comment: Significantly greater proportions of patients on alosetron showed need for interruption of treatment because of constipation (no stool for 4 consecutive days) than did patients on placebo, overall and in the subgroups with either diarrhea-predominant or alternating type of IBS. There were too few patients with pre-randomization constipation-predominant IBS to draw any conclusions.

Because of the case of apparent alosetron-induced hepatotoxicity of the worrisome kind in which both serum aminotransferases and total bilirubin were elevated in patient #4595 (described above), search was made for any other cases in this study in which the combination occurred. A tabulated listing of all abnormalities beyond "threshold" limits was found in Volume 157, pages 358-67, for total bilirubin (<31 μM), Alkaline phosphatase (>131 U/L), AST (>68 U/L), ALT (>68 U/L), albumin (<30 g/L), and total serum protein (<54 g/L). There were 5 patients on placebo who had at least one ALT over threshold (2x ULN), none of which were over 3x ULN and none associated with bilirubin elevation. One patient on placebo had isolated bilirubin elevation, with transaminase increases. On alosetron, there was 1 patient with isolated bilrubin increase, 2 ALT increases without bilirubin increase, and the cited patient #4595 who had both.

2. S3BA3002: 12-week, placebo-controlled study in women

The second of the two confirmatory, "pivotal" clinical studies that followed the dose-ranging studies in Europe and the United States, was actually completed first, by two months. It was designed with an identical protocol, carried out using the established dose of 1 mg alosetron b.i.d. before breakfast and before the evening meal, in women only, excluding women with constipation-predominant IBS. This restriction to a defined subset of patients with IBS followed the data resulting from the dose ranging studies S3BP12 and S3BA2001 in which it was discovered that men did not benefit from the dose of 1 mg b.i.d. that seemed to help women, especially those with diarrhea-predominant IBS. The retrospective redefinition of an endpoint as "adequate relief" of IBS symptoms resulted from the failure to see a significant reduction in the fraction of pain-free days in patients on alosetron in S3BA2001; this was reduced to a secondary efficacy measure in the protocols for S3BA3001 and S3BA 3002.

It was estimated that 300 patients for each of two study arms, 600 in all, would be needed to detect with 90% power at two-sided $\alpha = 0.05$ significance an increase of 15% in the proportion of patients on alosetron 1 mg b.i.d. who had "adequate relief" to about 55%, compared to 40% on placebo, allowing for 20% dropouts. Patients were to be adult women with IBS fulfilling Rome criteria (abdominal pain/discomfort relieved by defecation or associated with change in stool frequency or consistency for at least 6 months, and at least a 6-month history at least 2 days/week of > 3 stools/day or < 3/week; stools either lumpy-hard or loose-watery; straining or urgency or feeling of incomplete evacuation; passage of mucus; or bloating or distention). In addition, they had to show by daily telephone report during a two-week (at least 12 days) screening period pain/discomfort of moderate average severity (1.0 to 3.3 on a pain scale of 0 = none, 1 = mild, 2 = moderate, 3 = intense, and 4 = severe), and average stool consistency of at least 2.5 (on a scale of 0 = none, 1 = very hard, 2 = hard, 3= formed. 4 = loose, and 5 = watery). The women had to have had a normal sigmoid/colonoscopy, not have any major other system disease or any organic gastrointestinal disorder, not be using any of a long list of prohibited drugs affecting gastrointestinal motility or perceptions of pain. Data were to be gathered daily by touch-tone telephone in response to preprogrammed standard questions, and weekly questioning as to whether they had adequate relief the previous week (developed and analyzed by [redacted]. Adverse events were assessed by the investigators at visits at 4-week intervals during and once after the 12-week of study drug administration.

Of 1463 patients screened, 816 (56%) were excluded because pain severity or stool consistency scores were not met during the two-week screening period in 536 (low stool consistency score in 220, low pain score in 190, both in 96, high pain score in 27, and both high pain and low consistency scores in 3), other criteria were not met in 150, consent was withdrawn in 81, 13 failed to return, 11 had adverse events, and 25 had other miscellaneous reasons (Table S-6.1, Volume 167, page 130). This left 647 women who were randomized, 324 to alosetron 1 mg and 323 to placebo b.i.d. As predicted, a dropout rate of 20% was observed, 132 women leaving the study prematurely for a variety of reasons, principally adverse events , but substantial numbers also for "consent withdrawn" or "lost to follow-up" or "other" reasons. Study participants had a median age of 46 years, ranging from 19 to 83, were 93% Caucasian, 3% Black, 3% Hispanic, <1% Asian, and <1% Other. There were no significant differences in distribution of age, race,